

Summary

Since the introduction of cyclosporine into clinical practice five years ago, remarkable progress has been made in liver transplantation. Patient survival for both adults and children has improved from less than 35% at one year and 20% at 5 years to approximately 70% and 60% respectively.

The principal indications for transplantation in children have been biliary atresia, postnecrotic cirrhosis, and inborn errors of metabolism, with biliary atresia accounting for about half the cases. In adults, postnecrotic cirrhosis, primary biliary cirrhosis, inborn errors of metabolism, sclerosing cholangitis and primary liver tumors have been the most frequent reasons for liver replacement.

Although overall results have been good, there are important exceptions. First, transplantation for primary hepatic malignancy has been disappointing. Although early survival is excellent, most patients eventually have succumbed to recurrent tumor, often within one year after operation. Only the patients discovered to have an incidental hepatic tumor at the time of transplantation for other diseases such as postnecrotic cirrhosis have been free of tumor recurrence. Second, B-virus antigen carriers transplanted for postnecrotic cirrhosis have a high incidence of recurrent hepatitis after transplantation. Third, transplantation of infants continues to be complicated by a high incidence of hepatic artery thrombosis requiring urgent retransplantation.

Retransplantation for allograft rejection, technical complications (mostly hepatic artery thrombosis), or primary graft failure has been necessary in approximately 20% of patients. Survival is nearly 60% in patients retransplanted for rejection but is only about 40% for technical failures and 25% for primary graft failures.

Standardized techniques for removal and preservation of donor organs and organ implantation have also contributed to better results. Donor organs can be safely cooled by rapid aortic infusion of cold electrolyte solutions followed by an expeditious, bloodless dissection of the liver and en-bloc removal of the kidneys. This reduces the risk of warm ischemic injury during mobilization of the liver and kidneys and significantly reduces the time required to complete the donor operation. Routine use of a veno-venous bypass during the anhepatic phase of the recipient operation has reduced operative blood loss, postoperative renal failure, and cardiopulmonary complications and allowed successful transplantation of higher risk patients.

Patient selection is based on medical urgency and donor suitability as judged by ABO blood group and estimates of liver size. Although liver transplantation across ABO blood groups is usually successful, results have been best between ABO compatible donor-recipient pairs. A positive donor-specific cytotoxic antibody crossmatch has not been shown to be a significant barrier to transplantation of the liver.

Although liver transplantation is an expensive procedure, the cost must be weighed against the considerable cost associated with the care of those who would otherwise die of end stage liver disease. Rehabilitation after liver transplantation has been excellent and most patients return to active and productive lives.

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LIVER TRANSPLANTATION

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The principal indications for transplantation in children have been biliary atresia, postnecrotic cirrhosis, and inborn errors of metabolism. In adults, postnecrotic cirrhosis, inborn errors of metabolism, sclerosing cholangitis, and primary liver tumors have been the most frequent reasons for liver replacement.

Although overall results have been good, most tumor patients eventually have succumbed to recurrent tumor, often within one year. B-virus antigen carriers transplanted for postnecrotic cirrhosis have a high incidence of recurrent hepatitis after transplantation. Transplantation of infants continues to be complicated by a high incidence of hepatic artery thrombosis.

Retransplantation for allograft rejection, technical complications, or primary graft failure has been necessary in approximately 20% of cases.

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Although liver transplantation across ABO blood groups is usually successful, results have been best between ABO compatible donor_N^Irecipient pairs. A positive donor-specific cytotoxic antibody crossmatch has not been shown to be a significant barrier to transplantation of the liver. Rehabilitation after liver transplantation has been excellent. ✓

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HISTORICAL NOTES

7. ✓
The idea of transplanting the liver apparently was conceived first by C. Stewart Welch⁴⁰ in the early 1950^s. He reported research on transplanting an extra liver in a heterotopic site (such as the right paravertebral gutter) without disturbing the host liver. All of his experiments were without immunosuppression. Orthotopic liver replacement apparently was first conceived by Dr. Jack Cannon⁴¹ but his publication in 1956 gave no details and did not mention ^{✓ whether} ³⁴ if any of his animals (species unspecified) survived.

In the summer of 1958, two research programs on liver replacement were established independently, one at the Peter Bent Brigham Hospital in Boston⁴¹ and the other at Northwestern University in Chicago.^{39, 40} From these first efforts, the general requirements for liver transplantation, and the events of rejection in unmodified canine recipients were worked out. ✓

7. ✓
Protracted survival in experimental animals after liver transplantation was achieved in Denver in 1963 using azathioprine⁴¹ and soon after using antilymphocyte globulin (ALG).⁴² A number of animals from that original work survived for years.³⁹ ✓ The longest survivor lived a full canine lifetime and died almost 11 years after transplantation, having been without immunosuppression for all but 4 months of this time.

Renal transplantation became a practical form of treatment almost 25 years ago with the demonstration that azathioprine and steroids were synergistic.⁴³ Emboldened by successes with the kidney, the first clinical efforts at liver transplantation were made in Denver⁴³ in March, 1963, followed

Tx+ by similarly unsuccessful single attempts in Boston and in Paris.^{7, 22} The failure of the first seven patients to survive for as long as one month caused a moratorium to be declared until 1967. In 1966, ALG was added to the immunosuppressive armamentarium with trials in animals and in human kidney recipients.^{41, 42} Finally, in 1967, the first successful liver transplantations were carried out at the University of Colorado under azathioprine, steroids, and ALG.²² The longest survivor in the world today ^{has survived} is now almost 17 years. ^{post-trans}

Through the 1970's, further successes were achieved with liver transplantation, but between half and two-thirds of the recipients died within the first postoperative year.³⁶ The operation was so unpredictable and unreliable that it was justifiably considered to be an experimental operation as opposed to a service. This perception was drastically changed with the introduction of the new immunosuppressive agent cyclosporine by Calne et al in 1978^{3, 4} and with systematic combination of this agent with prednisone.^{37, 45} The first reports of nearly 80% ^{one} year survival of liver recipients⁴⁵ when this drug was combined with low doses of steroids ^{have} has been confirmed as the numbers of cases ^{have} has increased in the ensuing years.^{37, 38}

At the same time, technical improvements have played a significant role. It became obvious that optimal biliary tract reconstruction ^{involved} was anastomosis of the donor and recipient ducts over a T-tube (or stent) and that the only reasonable alternative was anastomosis of the donor duct to a defunctionalized limb of jejunum (Roux-en-Y).³⁹ These techniques greatly reduced bile fistulas and obstructions as well as the infectious complications that were resulting from imperfect drainage of the biliary tree. Later, the introduction of non-heparin veno-venous bypasses³⁵ made the operation a different one ^{than} the

high tension procedure which it had been previously. In turn, it became possible to train younger surgeons who could take the technology to new centers for further development.

Finally, the development of techniques for multiple organ procurement proved to be a crucial final step in making liver transplantation practical.

THE DECADE OF THE 1980's

During the past 5 years has seen a dramatic increase in the transplantation of extrarenal organs. By the end of 1985, 1787 heart, 1441 liver, 381 pancreas or islet cell, and 79 heart-lung transplantations had been performed in the United States (Fig 1,A). Approximately 45% of these transplants were done in 1985 (Fig 1,B).

The institutional resources and technical expertise required for heart transplantation are the most available and heart transplantation programs have been proliferating faster than those for the other extrarenal organs. Pancreas transplantation and heart-lung transplantation are still regarded as experimental and remain limited to investigational programs in a few major university transplant centers. Liver transplantation requires both exceptional surgical expertise and institutional support. Nearly half the liver transplantations performed in the United States have been done as part of the Denver-Pittsburgh series, but there has been a significant increase in the number of programs in the last few years (Fig 1,C).

1 THE IMPACT OF CYCLOSPORINE

T, + There can be no doubt that introduction of cyclosporine for clinical immunosuppression has been the most significant factor in the expansion of liver and heart transplantation.^{37, 38} For orthotopic liver transplantation, ^{✓ 1 =} one year patient survival has risen from 32.9% under conventional immunosuppression with azathioprine and high-dose steroids to 69.4% with cyclosporine and low-dose steroids in the Denver-Pittsburgh series (Fig ^{35 =} 2). Only 29 (17.1%) of the 170 patients who were managed with azathioprine and steroids remain alive, but nearly all of these patients are surviving more than ^{✓ 10} ten years after transplantation and are enjoying an excellent quality of life. Of the first 500 Denver-Pittsburgh patients transplanted using cyclosporine, 340 (68.0%) of the patients are alive, including 108 patients more than 3 years after transplantation.

For both azathioprine and cyclosporine-treated patients, the major patient mortality after liver transplantation has occurred within 6 months of transplantation (Fig ^{✓ 35 =} 2). Patient and graft loss beyond the first year after surgery has always been modest. Improved survival after liver transplantation has to a large extent depended upon effective prevention or treatment of acute rejection in the first ⁶ six months after transplantation and the major impact of cyclosporine has been to increase graft and patient survival in this critical early period through better control of rejection (Fig ^{35 = 2, 35 = 3} 2 and 3). Monoclonal anti-T-lymphocyte antibody (Orthoclone OKT-3(R), Ortho Pharmaceuticals, Raritan, NJ) has also proven highly effective in clinical trials for reversal of acute steroid-resistant cellular rejection in cyclosporine-treated patients.^{39, 40}

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Cyclosporine is a cyclic polypeptide derived from two strains of fungi. It can be administered intravenously or orally. Since absorption of the drug is highly variable and is poor in the early postoperative period, it is customary to give the drug intravenously for the first few days after transplantation followed by a period of combined intravenous and oral therapy with daily monitoring of trough serum or blood levels. Cyclosporine is lipid soluble and its gastrointestinal absorption is dependent upon bile and bile salts.⁴⁸ T-tube clamping is usually followed by a significant increase in cyclosporine absorption.¹ Also, the principal route of elimination of cyclosporine is by hepatic metabolism. Drugs such as phenobarbital, phenytoin, and rifampin, which are potent inducers of hepatic enzymes, can increase cyclosporine elimination and result in reduced blood levels. Erythromycin, an inhibitor of hepatic enzymes, can increase cyclosporine blood levels. Hepatic function and bile production after liver transplantation are variable, and therefore monitoring of drug levels is essential.

✓ In general patients receive 2 mg/kg of cyclosporine intravenously every eight hours immediately after transplantation. As soon as gastrointestinal function permits, oral cyclosporine, 17.5 mg/kg administered as a divided dose twice a day, is begun. Intravenous administration can be reduced to twice a day in many patients ^{after} oral therapy ^{has} is begun if drug levels are adequate. Within three to ⁶ ~~six~~ weeks of transplantation, doses of 10 mg/kg per day are ^{commonly} all that is required to maintain adequate drug levels. Renal excretion of cyclosporine is minimal, but the drug is nephrotoxic. Dosage may have to be reduced in patients with renal dysfunction. Cyclosporine is not removed by dialysis. In patients with severe renal dysfunction, a ²⁻³ ~~two~~ week course of

(Tx+)

monoclonal antibody therapy can permit sparing of cyclosporine until renal function recovers.

Conventional bacterial infections are better tolerated with cyclosporine than with azathioprine. This may be due to the selective action of cyclosporine on T-cells and to the lower doses of prednisone required with cyclosporine. Opportunistic fungal infections, Pneumocystis carini and Legionella pneumonias, and viral infections remain as significant problems.

(1) INDICATIONS FOR TRANSPLANTATION IN ADULTS

(Tx+)

The indications for liver transplantation in adults and children differ; and therefore it is useful to consider these groups separately. Of the 297 adults (patients over 19 years of age) in our first 500 cyclosporine-treated patients, 197 (66.3%) are living. One-year survival is 68.9% and five year survival is 54.8% (Fig. 4A). The most common indications for liver transplantation in adults have been chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis, inborn errors of metabolism, and primary liver tumors (Fig. 5).

Fig. 35-4
Fig. 35-5

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(2) Transplantation for primary liver cancer

(Tx+)

The first orthotopic human liver transplantations were done for hepatic tumors which could not be treated by subtotal resection. It was hoped that this patient population would be especially favorable for transplantation since portal hypertension and its complications are usually not present. Although early patient survival has been excellent, long term patient survival has been

poor (Fig 6B) because of a high rate of tumor recurrence in these immunosuppressed patients. (Fig 6B)

Our experience with transplantation for hepatic malignancy has recently been reviewed by Iwatsuki^{16,17} and colleagues. None of the 14 patients who were found to have an coincidental hepatic tumor at the time of transplantation for other diseases such as postnecrotic cirrhosis or biliary atresia, have died of recurrent tumor. All of these lesions would have been suitable for subtotal hepatic resection had not other disease of the liver^{had not} necessitated transplantation.

Forty-nine patients have been transplanted for liver tumors too extensive for conventional subtotal resection, including 21 patients transplanted using azathioprine-steroids and 28 transplanted with cyclosporine-steroids. Twenty-nine of these patients were transplanted for hepatocellular carcinomas. Thirty-two patients survived more than ³three months after surgery. Tumor has recurred in 20 patients (63%) and the liver graft is frequently the first site of recurrence. Less than half^{3 of} the patients remained tumor free for at least ¹one year. However, ^{5 of 7}6 of 7 patients with fibrolamellar hepatoma remained free of tumor for more than ¹one year. Although there is a high ultimate recurrence rate even for this variant of hepatocellular carcinoma, palliation is longer lasting.

Conventional chemo- and radiotherapy have been used in combination with total hepatic resection and transplantation in an effort to improve survival, but results have still been poor. ^{Surv}Two of our ⁴4 patients with non-fibrolamellar hepatoma treated with adriamycin and other chemotherapeutic agents,

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T₂ developed recurrence within a few months. The immunosuppression necessary to prevent graft rejection may accelerate the growth of extrahepatic nests of malignant cells unrecognizable at the time of transplantation. The high incidence of recurrence in the graft suggests that these cells are able to home back to the favorable environment of the liver. Nevertheless, the high survival of patients with coincidental malignancies demonstrates that long survival after transplantation in the presence of a hepatic malignancy is possible. Even in the patients with unresectable malignancy, significant palliation can be achieved, especially in patients with less aggressive tumors such as fibrolamellar hepatoma. ✓

Cirrhosis

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Cirrhosis is the most common indication for liver replacement in adults (Fig 5). ^{30%} Most of these are ^{✓ patients have} patients with chronic active hepatitis, but there are also small numbers of patients with cryptogenic cirrhosis or Laennec's cirrhosis. One year survival after transplantation for cirrhosis in adults is 67.2%, ^{at} but drops to 50.9% at 3 years (Fig 6,B). ^{30%} Until recently, survival for cirrhotic patients over 40 years of age has been poor, but this appears to relate to the coexistence of other risk factors in these patients rather than an effect of age itself. ^{20%} There is a significant incidence of recurrence of hepatitis in B-virus carriers. Alcoholic patients have always constituted a high risk group since their medical condition is often poor and recidivism is a constant concern. However, we continue to offer transplantation to carefully selected candidates with Laennec's cirrhosis.

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Primary biliary cirrhosis (PBC)

Primary biliary cirrhosis is the second leading indication for transplantation in adults. This is an uncommon disease, most often affecting late middle-aged women. The cause is unknown but it is considered to be an autoimmune disorder. Fatigue, jaundice, pruritis, hepatomegaly, and osteoporosis ("hepatic rickets") are characteristic features of the disorder, which may progress over many years. There is no effective medical therapy although a variety of agents including D-penicillamine, chlorambucil, colchicine, and even cyclosporine have been tried. A sudden increase in the rate of rise of serum bilirubin, progression of osteoporosis, or complications of portal hypertension (variceal bleeding, encephalopathy, intractable ascites) are indications for transplantation. The risk of recurrence of PBC after transplantation is unknown but the results so far are encouraging. Fifty-eight of the 83 patients transplanted for PBC are alive 3 months to 6 years after surgery. Actuarial survival is 68.4% at one and at 5 years (Fig 6,A). There have been no deaths and no confirmed recurrences of disease among the 42 patients surviving more than one year.

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Sclerosing cholangitis

Sclerosing cholangitis may occur in a primary form or in association with other diseases, especially inflammatory bowel disease. It is associated with an increased risk of carcinoma of the bile duct. Many of these patients have had attempts at surgical biliary diversion which complicates transplantation and should be avoided except in patients with well-defined extrahepatic lesions. Survival after transplantation has been improving and is presently

75.7% at one year (Fig 6³⁵A). The risk of late recurrence of disease or late development of bile duct cancer after transplantation for sclerosing cholangitis is not yet known. If proctocolectomy for associated bowel disease is indicated, it is best deferred until 3 to 6 months after liver transplantation. ✓

Inborn errors of metabolism

Twenty-three adults were transplanted for inborn errors of metabolism, including alpha-1³⁵-antitrypsin deficiency (11 cases), Wilson's disease (8 cases), hemochromatosis (2 cases), tyrosinemia (1 case), and cystic fibrosis (1 case). Survival in this group of patients has been good (Figures 6³⁵A and 8³⁵) with the exception of those patients who present in advanced stages of hepatic encephalopathy with acute hepatic decompensation from Wilson's disease. Mortality in the encephalopathic patient is 50%.

INDICATIONS FOR TRANSPLANTATION IN CHILDREN

One-hundred forty-three (70.4%) of the 203 children (age 18 and under) in the series are living with one year and five year actuarial survival at 70.4% and 67.7% (Fig 4³⁵A). As in adults, most of the mortality after liver transplantation in children is in the first 6 months after surgery.

Biliary atresia

Biliary atresia is the most common indication for liver replacement in children (Fig 5). Most of these patients have had previous operations, usually porto-enterostomies (Kasai procedure) and occasionally porto-systemic venous shunts, often with little if any benefit. Previous surgery in the hepatic hilum

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makes liver transplantation much more difficult and, for most children with biliary atresia, transplantation is the only genuine hope of long term survival. Conservative use of porto-enterostomy, however, is still appropriate. There is a severe shortage of donors for small children and a successful Kasai operation can stabilize the patient and buy valuable time. Although previous surgery is associated with an increased morbidity after liver transplantation, it has not been associated with an increased mortality. However, revisions of Kasai operations and stoma creation are rarely of significant benefit and greatly increase the difficulty of liver transplantation. Porto-systemic venous shunts should also be avoided whenever possible.

The results of liver transplantation for biliary atresia are very gratifying and long term survival has been excellent. ^{8.16} In our first 500 transplantations with cyclosporine, 68 of 99 patients with biliary atresia are surviving ³ three months to 6 years after surgery. Actuarial survival is 68.4% at ¹ one year and 66.7% at ⁵ five years (Fig ³⁵ 7). Only 4 of the 65 patients who have survived more than ¹ one year after transplantation for biliary atresia have died. Since only modest doses of prednisone are required with cyclosporine, growth and development in most of these children ^{are} is essentially normal. ⁴⁷ ✓

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Inborn errors of metabolism

The second most common indication for liver transplantation in children has been inborn errors of metabolism. Survival after liver transplantation for inborn errors of metabolism in children has been excellent (73.8% at ¹ one and ⁵ five years, Fig ³⁵⁻⁷ 7 and 8). Transplantation has been performed for alpha-1-
Fig. 35-7
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antitrypsin deficiency (27 cases), Wilson's disease (6 cases), tyrosinemia (5 cases), glycogen storage disease (5 cases), hypercholesterolemia (1 case) and sea-blue histiocyte syndrome (1 case). Two patients (one adolescent and one adult) have been transplanted for chronic active hepatitis contracted as a result of factor VIII therapy for hemophilia and the one survivor (the adolescent now 14 months ^{post=}since transplantation) appears to have been cured of his hemophilia.¹⁹ ✓

Two years ago a simultaneous heart-liver transplant was performed in Pittsburgh in a 6-year-old girl with homozygous familial hypercholesterolemia.^{24, 30} She had already required two coronary artery bypass operations and a mitral valve replacement for severe arteriosclerotic heart disease, but was failing despite this. A heart transplant was performed followed immediately by a liver transplant from the same donor. Although the liver appeared grossly normal, extensive studies of the child had indicated that the metabolic defect responsible for her disease was a defect in hepatic-based metabolism. Now more than ²two years after the double transplantation, the child is doing well and has a sustained improvement in her lipid and cholesterol profile.³ ✓

OTHER INDICATIONS IN ADULTS AND CHILDREN

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Most of the other pediatric liver transplantations in the Denver-Pittsburgh series have been done for cirrhosis (21 cases), familial cholestasis (14 cases), and neonatal hepatitis (giant cell hepatitis). One-year survival for these indications is over 75%.

Eight patients have been transplanted for Budd-Chiari syndrome with four survivors, all on permanent anti-coagulation. Extensive thrombectomy of ✓

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the portal system, the vena cava³ and iliofemoral veins may be required. Use of the venous bypass can be hazardous in this group of patients. After transplantation, these patients should be kept on permanent anticoagulation therapy.

Seven patients have been transplanted for acute hepatic necrosis. Four patients have survived, including ^{three} ~~3~~ patients now more than 2 years since transplantation. There is a chance of survival if patients are not in deep coma at the time of surgery or have been in coma only briefly. ✓

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SELECTION AND PREPARATION OF PATIENTS FOR TRANSPLANTATION

Since liver transplantation is a complex procedure³ it is often assumed that the evaluation and preparation of patients for surgery must also be complex. In fact, the evaluation of liver transplant candidates can often be accomplished quickly and at minimum^{cal} expense if the immediate needs of the patient are not confused with the research interests of the physicians. Most patients are referred to the transplant center with an established diagnosis and a poor prognosis without transplantation. A major gastrointestinal bleed, a history of repeated bouts of encephalopathy, progressive neuropathy, refractory ascites, a recent precipitous deterioration in liver function (e.g., a recent increase in the rate of rise of serum bilirubin), poor hepatic synthetic function (low serum albumin and elevated prothrombin time), rapid progression of bone disease, and severe wasting are indications for early transplantation. ✓

Many of these patients have been needlessly explored and subjected to useless if not mutilating biliary tract operations, questionable porto³systemic venous shunting, or unnecessary cholecystectomy or splenectomy. Variceal ✓

(Tx+) bleeding in patients awaiting transplantation is a common problem but can usually be managed by sclerotherapy. In the rare case ^{in which} where a venous shunt is required, meso⁺caval or spleno⁺renal shunts ^{rather than portocaval shunts} should be done, ~~not~~ porto-caval shunts. Splenectomy in patients with advanced cirrhosis and portal hypertension often results in portal vein thrombosis and may ruin the patient's chances for successful transplantation. Percutaneous needle biopsy is sufficient for tissue diagnosis in nearly all patients.

+ [✓] Computed tomographic
(CT) scans are useful to detect the presence of tumors, with or without extrahepatic extension. Laparotomy to rule out extrahepatic metastatic disease in candidates for transplantation for primary liver cancer is best carried out at the time ^{that} the patient is taken to the operating room for transplantation. If extrahepatic spread of disease is found, a backup candidate can then be quickly substituted.

A general evaluation of pulmonary, renal and cardiac function is appropriate to assess surgical risk and prepare the patient for surgery. Portal vein patency can be assessed by non⁺invasive ultrasound.¹⁹ We reserve invasive angiographic studies for patients whose portal vein cannot be visualized by ultrasound or in patients with previous venous shunts in whom it is important to assess the status of both the shunt and the portal vein.

The patient's weight, height, ABO blood group and ultrasound measurements of liver size are important in donor selection. Most patients with post⁺necrotic cirrhosis have a small liver, whereas patients with sclerosing cholangitis and primary biliary cirrhosis usually have substantial hepatomegaly. Liver transplantation can be successfully done across ABO blood groups and [✓]

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in the presence of pre-formed anti-donor antibody without significant risk of hyperacute rejection. Survival of grafts in patients with preformed anti-donor antibody or high panel reactive antibody (Fig 9) is the same or better than survival of grafts in patients without antibody.³⁵ However, long-term graft survival for ABO matched grafts (Fig 10) has been better than for ABO compatible but non-identical or ABO incompatible grafts.³⁵ That^o Thus, we recommend that ABO compatible donors be used except in urgent situations or for young children where donor availability is a critical problem.

The improved patient survival offered with cyclosporine has encouraged referral of better candidates and has expanded the indications for liver transplantation. For example, just a few years ago, liver transplantation was limited to patients ^{younger than} under 55 years of age. However, survival of the 41 patients ^{older than} over 50 years of age in our first 500 cyclosporine-treated patients has been just as good as survival for 256 patients between 18 and 49 years ^{face} (Fig 4,C). Six of the ^{seven} 7 patients over the age of 60 ^{years} have survived, including one patient 67 years old at the time of transplantation. ✓

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Predicting which patients will succeed and which will fail based on pre-operative risk factors is ^a difficult ^{tasks and associated}. Shaw recently performed a retrospective analysis of 118 liver transplantations in Pittsburgh over a ⁴ four year period to determine whether survival in the first ⁶ six months could be predicted on the basis of preoperative condition.³⁹ Variables coded in the analysis included mental status, malnutrition, ascites, previous surgery, and complications (variceal bleeding, biliary sepsis, or spontaneous bacterial peritonitis). Operative blood loss was also analyzed. The analysis produced a sigmoidal curve with most patients on the steep slope of the curve between inflection

Tx+ points. Thus, it is difficult for most patients to predict early outcome based on these preoperative factors. Patients in deep coma at the time of transplantation, however, rarely survive unless their condition can be improved to the point that they are awake and off the respirator when taken to the operating room. Nevertheless, even patients in acute hepatic failure and coma have survived if transplanted quickly.

Given this unpredictability of survival, we continue to select patients for transplantation based on liver size, ABO blood group, and medical urgency. Only patients in deep, irreversible, subacute or chronic coma have little chance of survival.

1 ORGAN PROCUREMENT

Tx+ The development of effective techniques for multiple organ recovery has been essential to the expansion of renal, liver, and heart transplantation.^{27, 28, 34}

24 An insufficient supply of brain-dead organ donors remains the single greatest limiting factor in solid organ transplantation.

Public awareness of the progress in organ transplantation and the need for organ donors has resulted from media attention, professionally sponsored educational programs, and government interest. Our voluntary system of organ donation has for the most part worked well. The public's response has been highly supportive, but significant resistance to organ donation has come from physician apathy or reluctance to raise the issue of donation with potential donor families. Legislation to require hospitals to request permission for organ donation has been passed in several states in the past year and is under active consideration by many ~~more~~ other states.

1 TECHNICAL CONSIDERATIONS

2 Donor hepatectomy

Fig 1
A well-preserved, promptly functioning allograft is essential for successful liver transplantation. Techniques have been developed which permit the liver, kidneys and thoracic viscera to be obtained from a single donor.^{33, 34}

In the traditional procurement technique, the abdomen and thorax are entered through a complete midline sternal splitting incision. The left lateral segment of the liver is mobilized and the aorta encircled just above or below the diaphragm.

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Great care must be taken to identify and deal with the frequent variations in hepatic arterial supply. The gastrohepatic ligament is palpated and inspected for the presence of a branch of the left gastric artery to the liver (Fig 11) which, if present, is preserved by dissection of the left gastric artery back to its origin from the celiac axis. The division of the left gastric artery to the greater curvature of the stomach can then be safely ligated and divided. The right hepatic artery (or, rarely, the common hepatic artery) may originate from the superior mesenteric artery and lie posterior to the portal vein. This artery must be preserved in continuity with the proximal superior mesenteric artery. Special techniques have been developed for reconstruction of livers with multiple arteries (Fig 11).³⁵

Fig 35-11

Once the preliminary dissection is completed, cannulas are inserted in the abdominal aorta and inferior vena cava and cold Ringer's lactate is slowly infused through the portal vein cannula to cool the donor to $30-32^{\circ}\text{C}$ (Fig 12). The central venous pressure and consistency of the liver are carefully monitored, and the inferior vena cava cannula is opened as needed to remove excess volume and prevent hepatic congestion. Once the liver is cool, or if the donor becomes unstable, the aorta is crossclamped at the diaphragm and cold Collins² solution is infused through the aortic and portal vein cannulas. The inferior vena cava is divided at its junction with the right atrium.

After a brief but thorough flush of the liver, the aorta is divided proximal and distal to the origin of the hepatic arterial supply taking care not to injure the renal arteries. A clamp is placed just proximal to the renal vessels to permit continued cold perfusion of the kidneys after division of the upper aorta. The diaphragm is cut leaving a wide cuff containing the suprahepatic vena cava. The infrahepatic vena cava is then mobilized and entered anteriorly just above the renal veins. The orifices of the renal veins can be seen inside the opened vena cava which is then safely divided. The liver is taken to the back table, given a final flush of Collins² solution through the portal vein, and packaged for transfer to the recipient hospital.

The kidneys can be rapidly excised en²block and separated on the back table. The left renal vein is divided at its origin from the vena cava. The vena cava should not be split in half, but rather should be left intact attached to the right renal vein for use in providing additional length.

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The aorto-iliac arteries and the iliac veins are also harvested. These grafts are often necessary for reconstruction of the arterial supply and portal vein in recipients with inadequate native vessels. Iliac vein segments can also be grafted to the right renal vein to add length during transplantation of the right kidney. ✓

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The standard technique of procurement can be modified to permit rapid removal of the liver as may be necessary in an unstable donor. ✓ No preliminary dissection is performed except encirclement of the proximal aorta and placement of distal aortic and vena cava cannulae. If the heart is to be taken, it is then prepared and when the thoracic team is ready to arrest circulation, the proximal aorta is crossclamped. A rapid infusion of cold Collins² solution is then begun through the aortic cannula (Fig³⁵ 13). The inferior vena cava is divided at its junction with the right atrium. The heart is then removed while the liver continues to flush. The intestines and portal vein will blanch within 2 to 3 minutes and the liver will be palpably cold. In adults, 2 to 3 liters of flush are sufficient to cool the liver to a cryoprotective temperature of less than 28°C. Once this has been achieved, the aortic flush is slowed and the hepatic arterial supply and hilum is dissected in a bloodless field. The same care must be taken to identify and preserve arterial anomalies as with the standard technique. The liver is then excised in a manner similar to the standard method leaving a cuff of diaphragm and the adrenal gland attached to the hepatic portion of the vena cava. In experienced hands, the donor hepatectomy can be performed in only half an hour by this method. ✓

✓ Fig. 35-13

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The final preparation of the allograft occurs on a back table in the recipient operating room. The adrenal gland and excess diaphragm are removed, and the vascular cuffs are prepared for anastomosis. All technical anomalies are reported to the recipient surgeon so that he may make any changes in recipient technique necessary to accommodate the graft.

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The Recipient Operation

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The recipient hepatectomy is often the most difficult part of the liver transplant procedure, and there is no single best method. Individual dissection of hepatic hilar structures may be impossible because of previous surgery or because of massive formation of varices. Mobilization of the liver from the hepatic fossa may result in massive hemorrhage if the hepatic arterial and portal venous blood supply have not first been controlled.

Occlusion of the vena cava and portal vein without bypass may result in cardiovascular instability, splanchnic and renal venous hypertension, and increased hemorrhage from thin-walled venous collaterals. Since 1983, we have routinely used a pump-driven veno-venous bypass system without systemic heparinization during the anhepatic phase of the recipient operation. We believe that this has contributed to a significant reduction in morbidity and mortality. Use of the bypass has permitted modifications in the technique of recipient hepatectomy, decreased transfusion and fluid requirements, and reduced cardiopulmonary and renal complications.

When possible, the individual structures in the hepatic hilum are skeletonized, but no other dissection is necessary. Bypass is then established

(T₂+) by placement of cannulas in the portal vein and sapheno-femoral vein. Return to the superior vena cava can usually be done through a cannula in the axillary vein. If the hilar dissection is difficult, a vascular clamp is placed across all the hilar structures which are then transected (Fig 14). The individual structures are then identified, dissected back, and the portal vein is cannulated. ✓

Division and cannulation of the portal vein greatly facilitates mobilization of the liver from the hepatic fossa and dissection of the infrahepatic vena cava. The triangular ligaments and and peritoneal reflections that make up the coronary ligament are cut and the right lobe of the liver is elevated into the wound. The suprahepatic and infrahepatic segments of the vena cava are then encircled. If it is not possible to encircle either the upper or lower vena cava, the liver can be shelled out from above or below as shown in Figures 35-15 35-16
Fig 15 and 16 ✓

Once the liver has been removed, use of the veno-venous bypass provides time to close the raw areas created during the hepatectomy as shown in Figure 35-17. This will minimize bleeding during performance of the vascular anastomoses. Adequate vena cava cuffs and sufficient length of portal vein must have been developed before the graft is brought into the field for anastomosis.

The anastomosis of the suprahepatic vena cava is performed first, followed by the infrahepatic vena cava. Near completion of the the lower cava anastomosis, the liver is flushed with cold lactated Ringer's solution to remove entrapped air and concentrated potassium. The portal bypass cannula is then ✓

(Tx) removed, leaving the patient on vena cava bypass while the portal vein is reconstructed. The liver is then revascularized with portal flow, and all remaining bypass cannulae^s are removed. After reasonable hemostasis is obtained, the hepatic artery is reconstructed.

Successful reconstruction of the portal venous and hepatic arterial circulations demands flawless technique. Failure of either anastomosis usually leads to patient death or retransplantation. A modified continuous suture technique with 6-0 or 7-0 polypropylene suture is used such that the knot is tied a significant distance from the vessel wall.³⁵ This permits the vessel to distend to full caliber as the suture recedes back into the vessel and redistributes itself after restoration of flow. A single interrupted suture placed where the two ends of the continuous suture meet prevents separation of the vessel at the growth factor (Fig 18).

Direct anastomosis of the graft to the recipient hepatic artery is often not possible because of inadequate size, disease, or injury of the native artery. Alternative methods of reconstruction must be used in these cases.³⁶ Our preferred method is to use a segment of donor iliac artery^{that} which is anastomosed to the infrarenal aorta and tunneled under the pancreas and duodenum to reach the graft. Conduits of donor aorta left in continuity with the celiac axis and hepatic artery and anastomosed to the recipient infrarenal aorta have also been used in small children.

Before the biliary reconstruction is attempted, complete hemostasis should be obtained. In recent years direct duct-to-duct reconstruction over a T-tube³⁵ (Fig 19A) has been our preferred method of biliary reconstruction.

When this is not possible, such as in patients with disease of the extrahepatic biliary system, Roux-en-Y choledochojejunostomy over an internal stent is used (Fig 19B). ✓

POSTOPERATIVE CARE AND COMPLICATIONS

Initial Care

After surgery, initial care is similar to that for other patients undergoing a major general surgical procedure. The patient is kept in intensive care until ^{✓ alert or stable} alert, extubated, and hemodynamically stable. Many patients are ready to return to the regular hospital floor within 48 hours after transplantation. Antibiotic prophylaxis for biliary tract organisms (^{✓ Escherichia} Klebsiella, E. coli, and enterococci) is begun before surgery and continued for 5 days.

Nearly all patients leave the operating room with a significant excess of fluid₃ and most patients will have oliguria in the first ^{✓ 24 = 48} 24-48-hour period. Diuretics and colloid are often required. Vigorous use of crystalloid can easily result in pulmonary edema. Fresh frozen plasma (FFP) should be used with restraint ^{✓ because} since overzealous correction of clotting parameters may contribute to postoperative hepatic artery thrombosis. We generally avoid use of FFP unless the prothrombin time is persistently over 25 seconds or there is evidence of major ongoing blood loss with abnormal clotting parameters.

It is best to give potassium as bolus when needed rather than add it to the maintenance ^{✓ intravenous} IV fluids. Graft necrosis (primary non-function or hepatic artery thrombosis) can result in ^{✓ unpredictable} sudden increases in serum potassium.

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Children can rapidly develop low ionized calcium levels and hypo_{Ca} or hyperglycemia after liver transplantation. Thus, glucose and ionized calcium levels must be monitored closely during the first 48 hours.

Mental status, prothrombin time, and urine output are important indicators of the quality of early graft function. Narcotic and other medications ^{that} which may interfere with the evaluation of mental status are contraindicated. Primary graft failure occurs infrequently but is a very serious complication. The patient decompensates quickly and will show markedly abnormal liver function, coagulopathy, oliguria, and severe ^{central nervous system} CNS changes. Stage IV coma, alkalosis, hyperkalemia, and hypoglycemia characterize the terminal phase of this acute hepatic decompensation. Avoid giving any potassium, give ^{FFP} fresh frozen plasma every 4 to 6 hours, and keep the gastric ^{more} pH less than 5. Urgent retransplantation is required.

Hypertension is a common problem in the postoperative patient. Hydralazine and beta-blockers (labetalol, ^{propranolol}) are first-line drugs. Minoxidil (Loniten), clonidine (Catapres), and captopril (Capoten, often preferred for children) are alternatives in patients requiring other agents. Avoid methyldopa (Aldomet), which is hepatotoxic. Intravenous nitroglycerine can be used when appropriate for patients in the ^{intensive care unit} ICU. Sodium nitroprusside must be used with caution because of the potential for cyanide toxicity. Nifedipine (Procardia), 10 mg, administered under the tongue, is useful in an emergency.

In cases of refractory hypertension, labetalol (trandate normodyne), a beta- and alpha- adrenergic blocking drug with selective action on peripheral

Tx+

vascular receptors, can be given intravenously. The drug must be given by a physician with continuous blood pressure monitoring in the intensive care unit. It is given in ⁱⁿ 20 mg doses over 2 minutes and may be repeated every 10 minutes up to a total of 300 mg or can be administered as a continuous intravenous infusion at 2 mg/min, adjusted according to the blood pressure. ✓

2

Immunosuppression and Rejection

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Cyclosporine therapy has been discussed previously. Patients with persistent oliguria or elevated serum creatinine require reduction of cyclosporine dosage. In cases of severe renal failure, cyclosporine is discontinued and treatment with monoclonal OKT-3 antibody is substituted for as long as ²~~two~~ weeks to allow renal function to recover.

The patient is given ^{1 g}~~one gram~~ of methylprednisolone intraoperatively and then begun on a steroid taper after surgery. Adults are begun on 200 mg per day given in (4) divided doses and tapered 40 mg per day until a maintenance dose of 20 mg per day is reached. Children are begun at 100 mg per day and ^{are} tapered by 20 mg per day. Very small children are maintained on only ^{mg to} 10-15 mg per day. As soon as oral intake is established, oral prednisone is substituted for the intravenous steroid. ✓

Hyperacute rejection of the liver is a controversial entity, and, if it exists, is a rare event. Acute allograft rejection usually occurs 7 to 21 days after operation, but can occur at any time. Early "accelerated" rejection is

occasionally seen. Liver biopsy may be required to distinguish between early rejection and ischemic injury.

Rejection is most commonly manifested by malaise, fever, graft swelling and tenderness, and diminished graft function. A rise in bilirubin and transaminases is usually seen and T-tube biliary drainage may be thin and light in color. Clinical rejection is treated initially by a ¹/₃ gram IV bolus of methylprednisolone followed by a complete recycle of the postoperative steroid taper. If response is poor, biopsy and treatment with monoclonal antibody should be considered.

Monoclonal mouse anti-human thymocyte globulin (OKT-3) has been approved for clinical use by the U.S. Food and Drug Administration. It is used for the treatment of acute steroid-resistant rejection or for sparing of cyclosporine in toxic patients. It is given as a single daily dose of 5 mg IV over 5 minutes (2.5 mg in children less than 30 kg). Benadryl and Solucortef are given ^{prior} ~~before~~ ^{it to} reduce unpleasant reactions. ^{Complete blood count} (CBC), hematocrit, platelet count, and T-cell ratios are monitored during therapy.

Chills and fever are common with the first few doses of OKT-3. Bronchospasm, hypotension, chest pain, nausea, vomiting, and diarrhea may also occur. Pulmonary edema can occur in patients who are fluid overloaded. Acute respiratory symptoms ("anaphylactoid reactions") or anaphylaxis, manifested by joint pains, shortness of breath, and hypotension, may occur and require stopping the drug and administering epinephrine, steroids, and oxygen.

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Therapy is usually continued for 10 to 14 days. Patients may develop antibodies to the mouse protein with subsequent loss of efficacy. ✓

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Post-transplant hepatitis

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Infection is responsible for much of the morbidity and mortality after liver transplantation and it can be difficult to distinguish rejection from postoperative viral hepatitis. Cytomegalovirus (CMV) infection of the liver is the most common troublesome offender. It is diagnosed by serologic changes and/or isolation of the virus. Liver biopsy may show the typical inclusion bodies in the hepatocytes but biopsy material should always be cultured.

CMV infection may be primary, as established by seroconversion, or by reactivation of prior infection, as documented by a four fold or greater rise in antibody titer. Many CMV infections are self-limited if immunosuppression is managed with restraint. Steroid maintenance should be reduced and cyclosporine levels kept as low as possible. ✓

Hepatitis B-virus, adenovirus, and herpes virus are other less common offenders. Hepatitis B is also often self-limited and managed by reduced immunosuppressive therapy. Herpes and adenovirus graft hepatitis have a poorer prognosis and early retransplantation may offer the best chance of survival for patients with these infections. ✓

2
Technical complications

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Surgical mortality (death within 30 days of operation) has significantly declined since 1980 and is currently less than 10% (Fig 20). Technical complications are still responsible for a significant portion of the morbidity and mortality after liver transplantation. Our first 393 transplantations in 313 cyclosporine-treated patients were recently reviewed by Lerut³⁵ and colleagues¹⁸. In 393 transplantations there were 87 (22.1%) technical complications with 24 directly related deaths, including 52 biliary tract complications (13.2%) responsible for 5 deaths and 27 hepatic artery thromboses (6.8%) responsible for 16 deaths.

Direct duct-to-duct biliary reconstruction over a T-tube or Roux-en-Y choledochojejunostomy over and internal stent^{was} were successful in 305 of 334 (91.3%) grafts. Failures of duct-to-duct reconstruction are best managed by conversion to Roux-en-Y choledochojejunostomy.

Hepatic arterial thrombosis is the most common technical complication requiring retransplantation and accounts for nearly 40% of the retransplantations in children (Fig 21). It is the most common indication for retransplantation in children³⁵ under 2 years of age. Despite this, survival of children^{younger than} under 2 years of age has been no different than^{that} survival of older children (Fig 4B).

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Fever with gram-negative septicemia is almost pathognomonic of hepatic artery thrombosis and the clinical presentation generally follows one of three patterns: acute hepatic gangrene, delayed biliary fistula, or relapsing bacteremia.⁴⁶ The ischemic injury to the biliary tree often results

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intrahepatic abscess formation or biliary fistula. Doppler ultrasound studies are useful in assessing the patency of the hepatic artery.²³ If pulsations are not well visualized, an arteriogram is indicated. Ultrasound or CT scans may demonstrate abscesses in the hepatic parenchyma. A few patients, mostly small children, have survived hepatic artery thrombosis without retransplantation, but for most patients, replacement of the graft is eventually, if not urgently, required.

RETRANSPLANTATION

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In our first 500 cyclosporine treated patients, 147 (22.7%) have required retransplantation for allograft rejection (53.1%), technical complications (27.9%), or primary graft failure (19.0%) (Fig 21). Fortunately, survival after retransplantation has also improved. Patient survival after retransplantation for loss of a first transplant, regardless of cause, is 46.4% at one year, and for loss of a second graft, is 53.4% at one year (Fig 22, A).
Fig 22-21
22-22

For patients retransplanted for loss of a first graft to rejection, one year survival is 59.5% and for technical failures (mostly hepatic artery thrombosis), is 43.1% (Fig 22, B). Primary non-function is a devastating complication, since the patient is in acute hepatic failure, is often septic, and is in urgent need of another liver. One year survival after retransplantation for primary failure of a first transplant is only 27.4% (Fig 22, B).

CONCLUSION

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The past five years has seen liver transplantation accepted as the treatment of choice for most causes of end stage liver failure in children and

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adults. Many major commercial and Blue Cross medical insurance programs now provide coverage for this procedure. Most of the patients who survive the operation return to a relatively normal lifestyle within one year of operation. Although the immediate costs of the operation are considerable, averaging over \$150,000 for medical costs and family expenses, the reward is also high. Death from liver failure is expensive also and nothing is returned to society. Most of the patients who require liver transplantation are either children soon to enter or adults in the productive years of life. The worth to society of the advances in knowledge that have and will continue to accrue from programs in organ transplantation are incalculable.

Liver transplantation is often cited by critics as an example of "high-tech" medicine which contributes to the escalation of health care costs. Luebs²⁰ has replied, "when the cost of health care in our society is attacked as being too high, one must ask "compared to what?" Is it too high compared with the cost of national drug and alcohol consumption? Is it too high compared with our nation's defense bill or our payment of interest on the national debt?...the true cost of health care, although taking a large portion of our nation's gross national product, is reasonable in a society concerned with suffering and the quality of life."

Organ transplantation depends upon public goodwill since it is the public that provides both essential resources, money and organs. The public's enthusiastic support of organ donation and its charitable financial support of transplantation programs is a clear signal that the nation has not lost its traditional commitment to the relief of individual suffering. ✓

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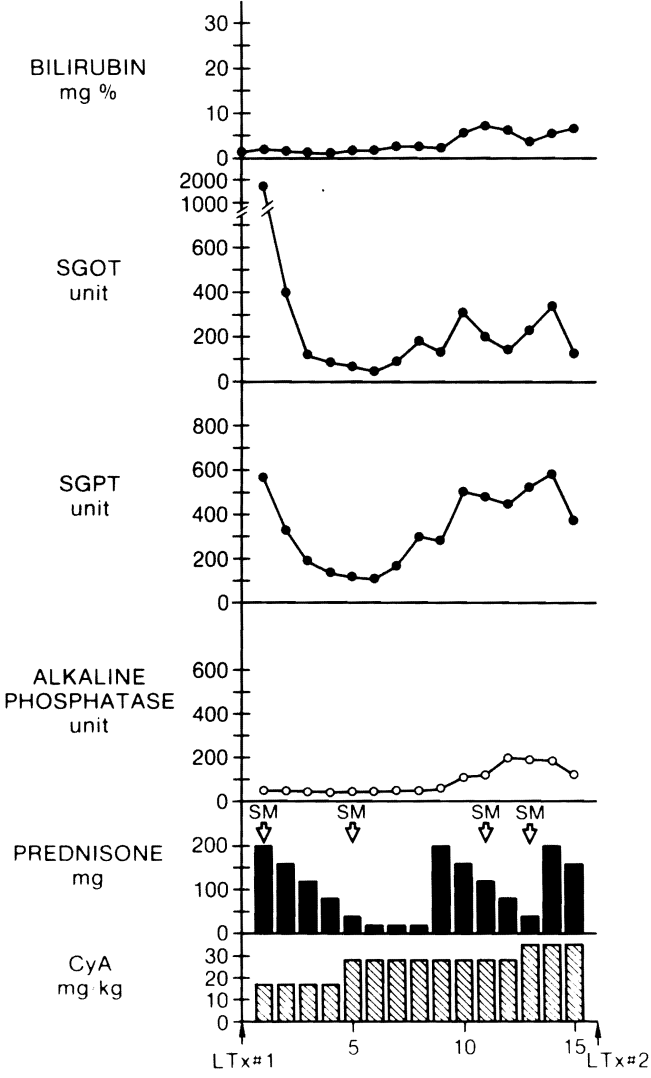
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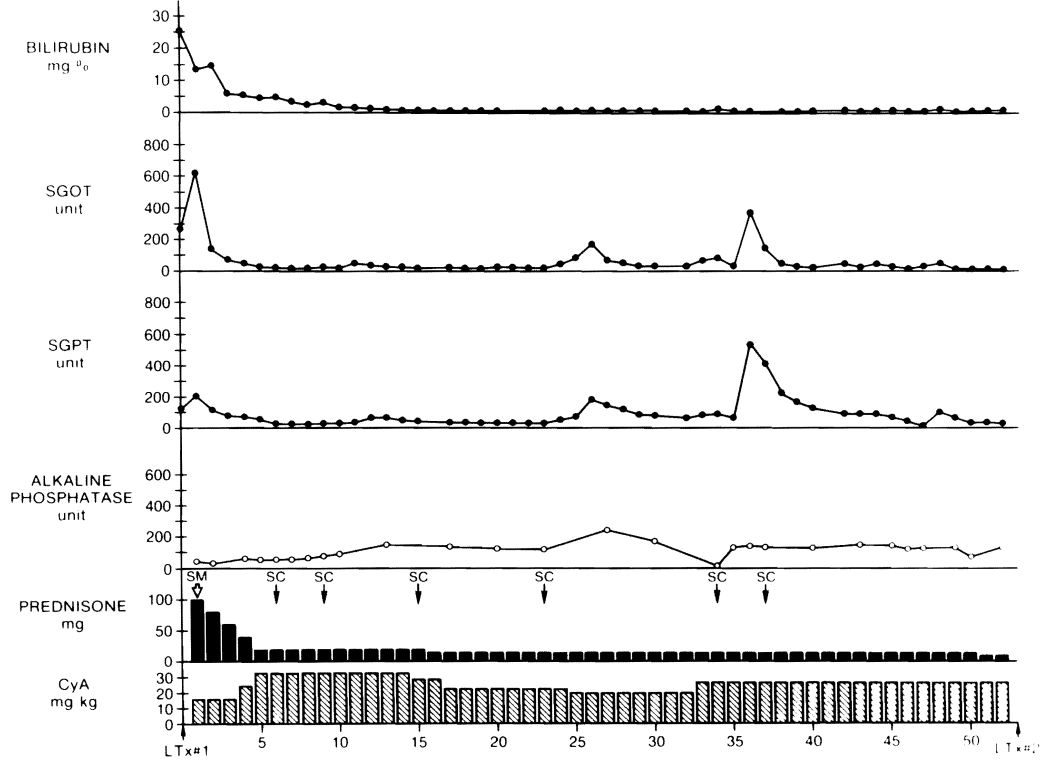
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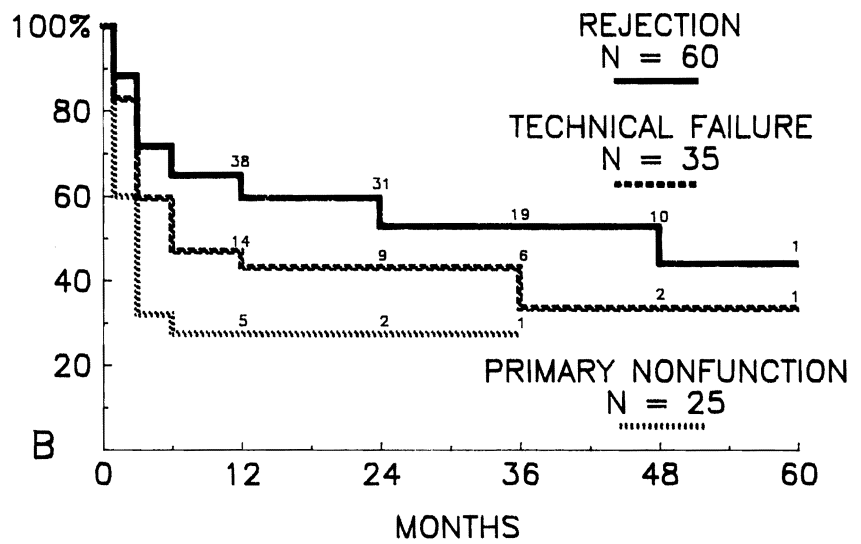
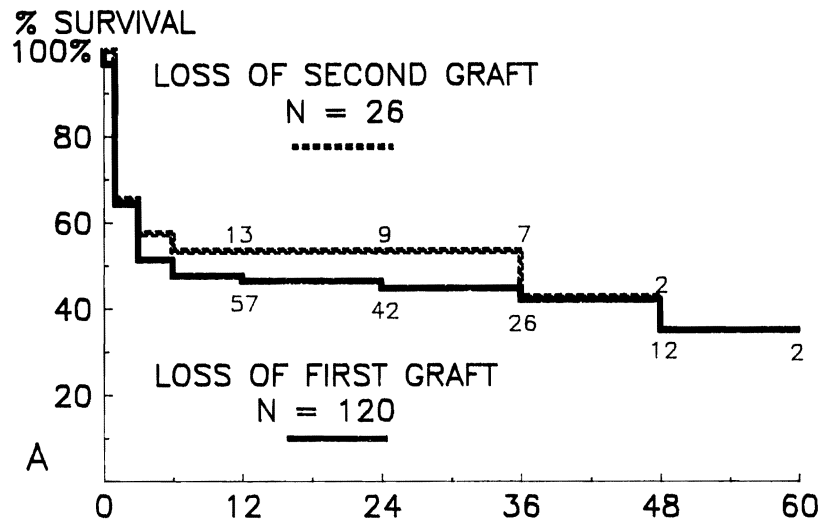
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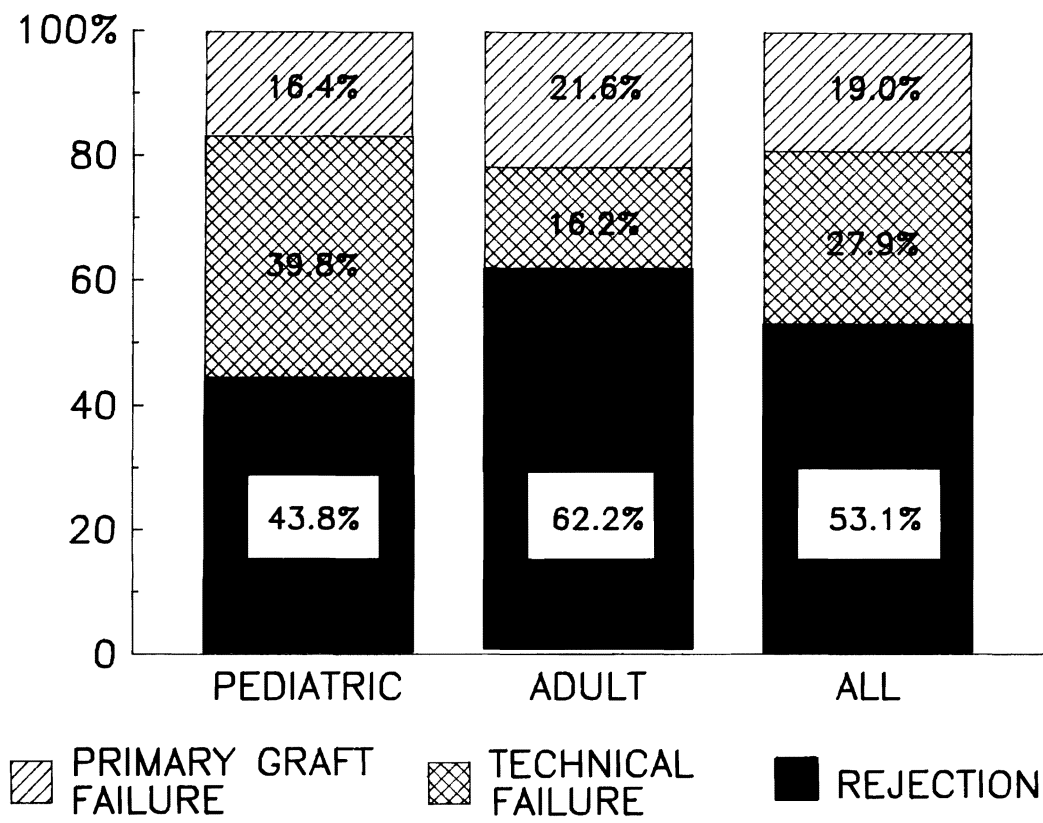
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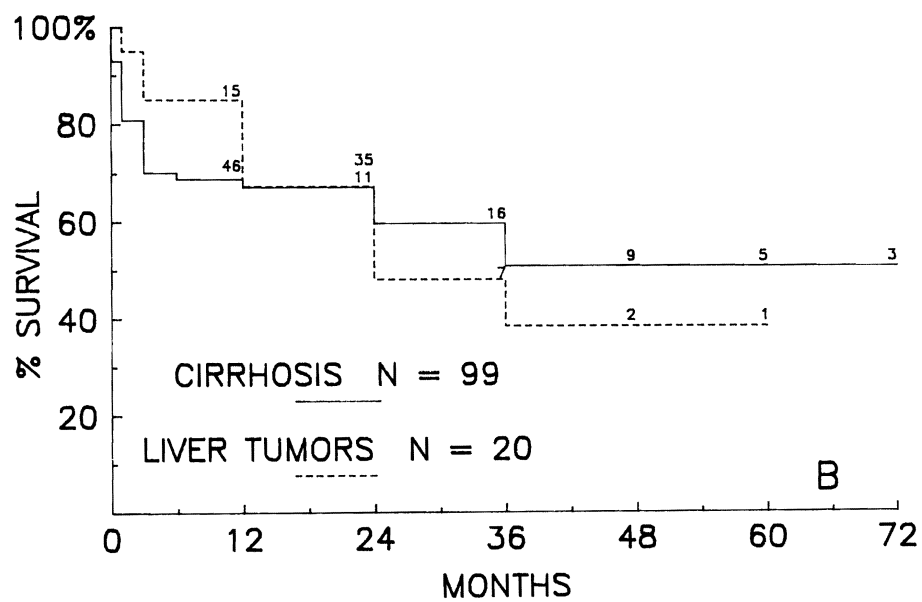
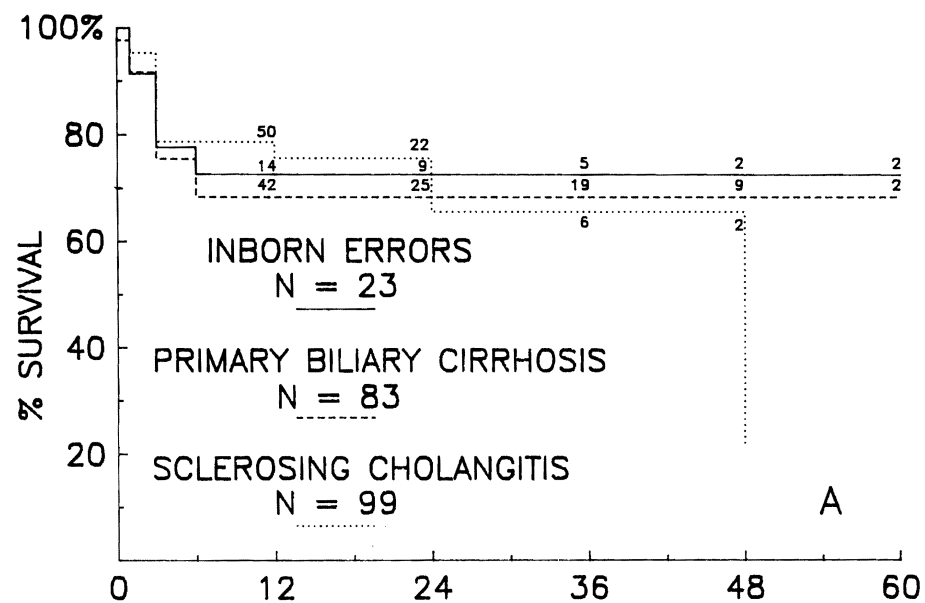


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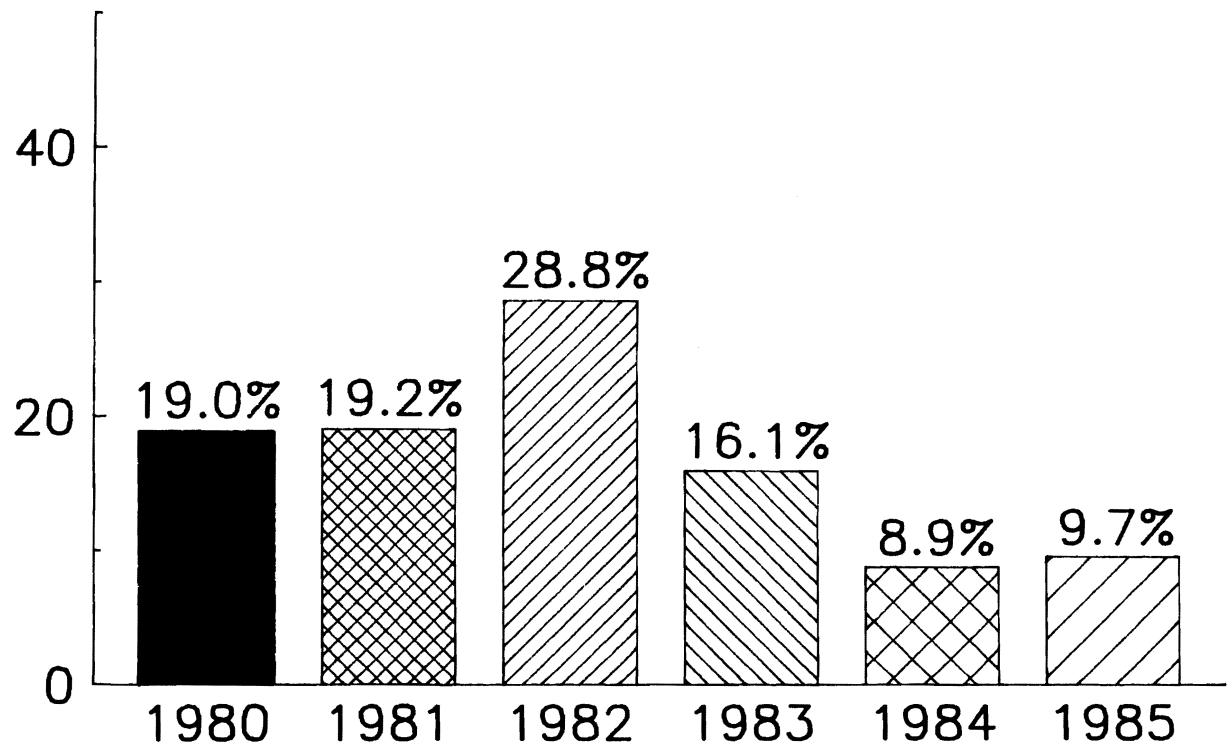


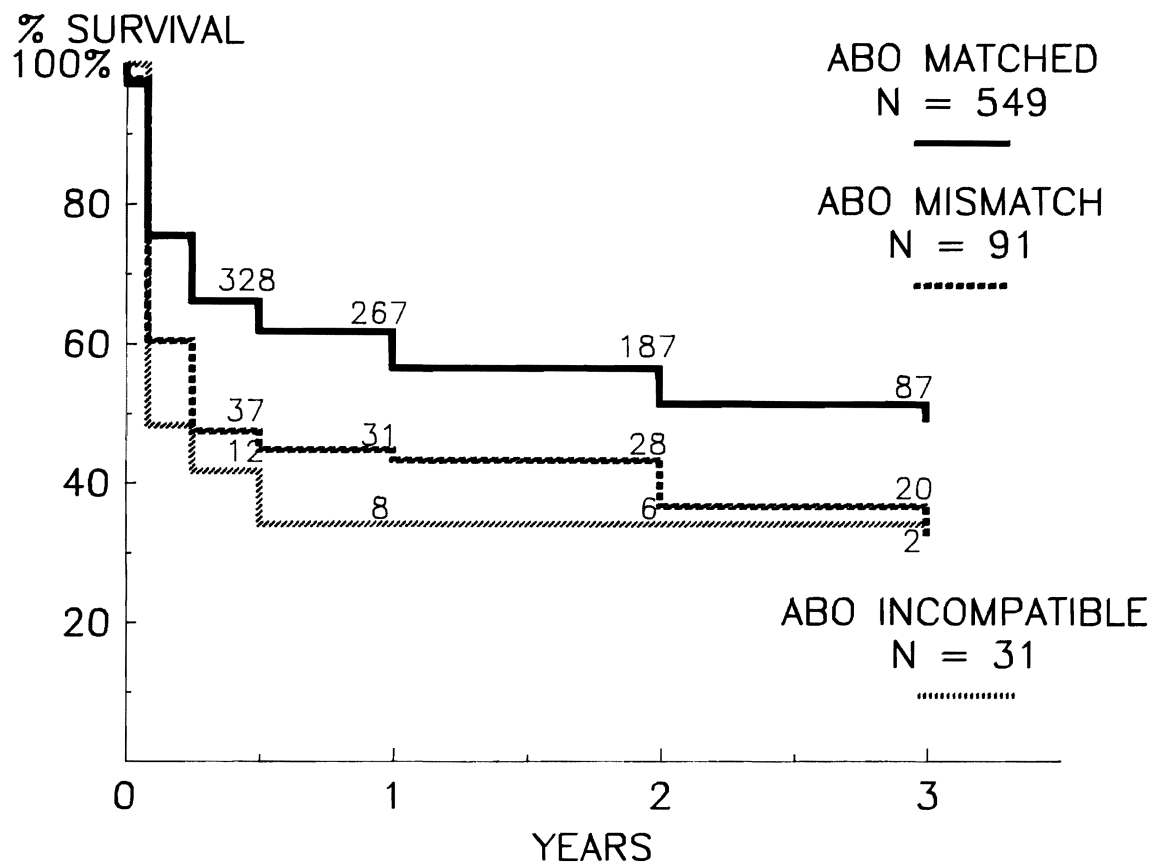


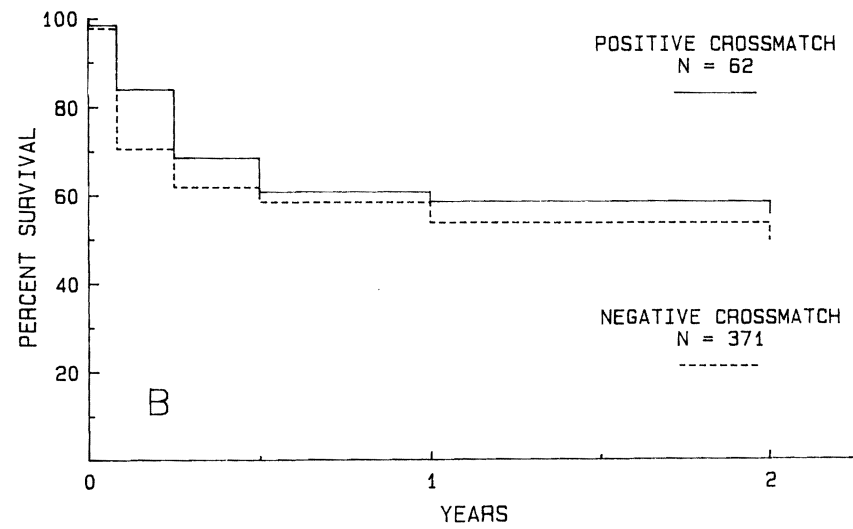
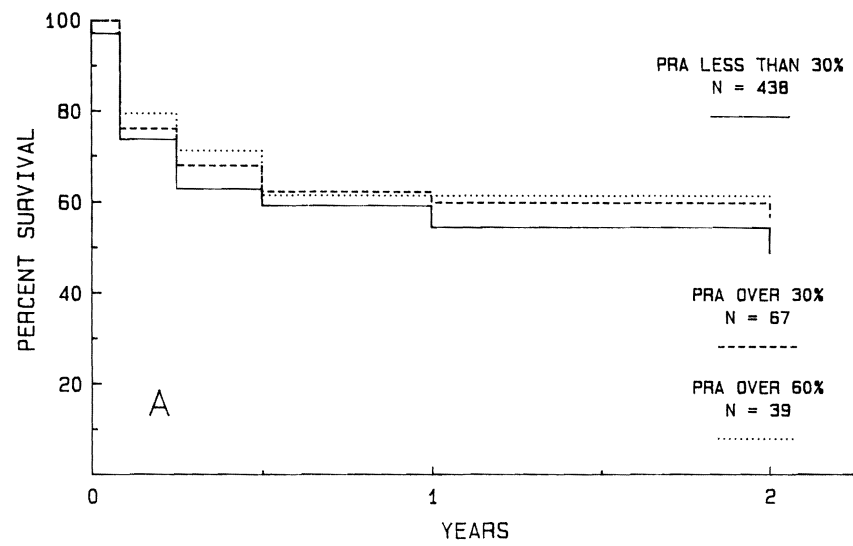


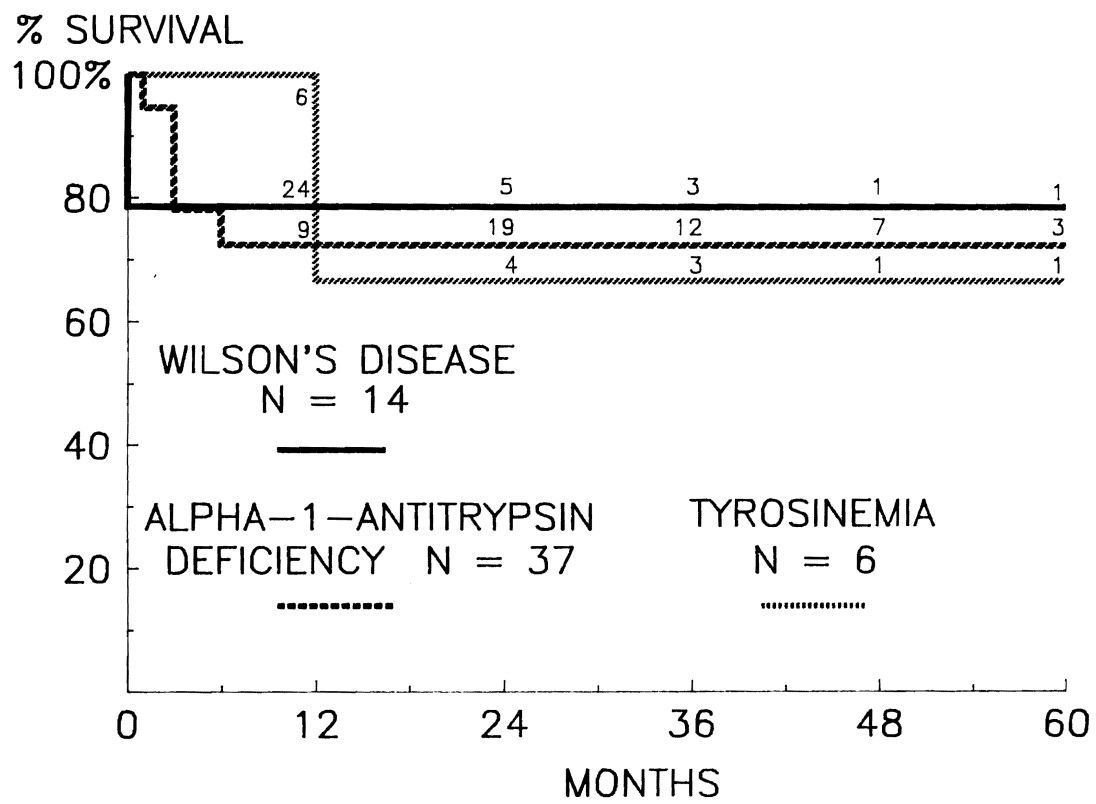


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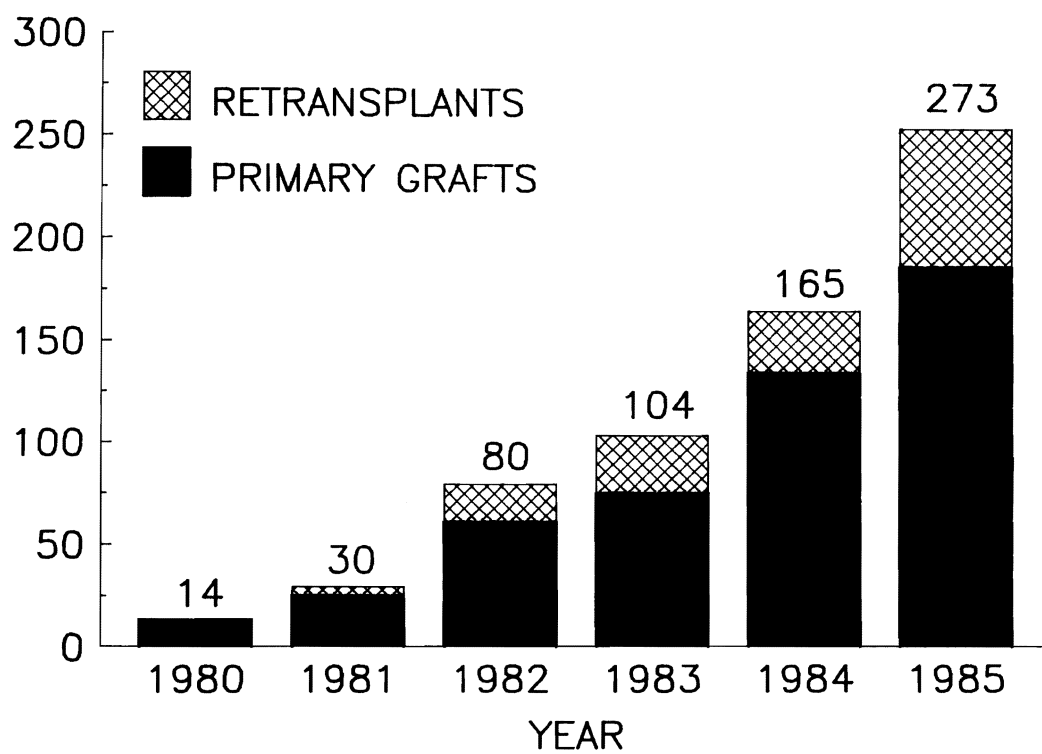


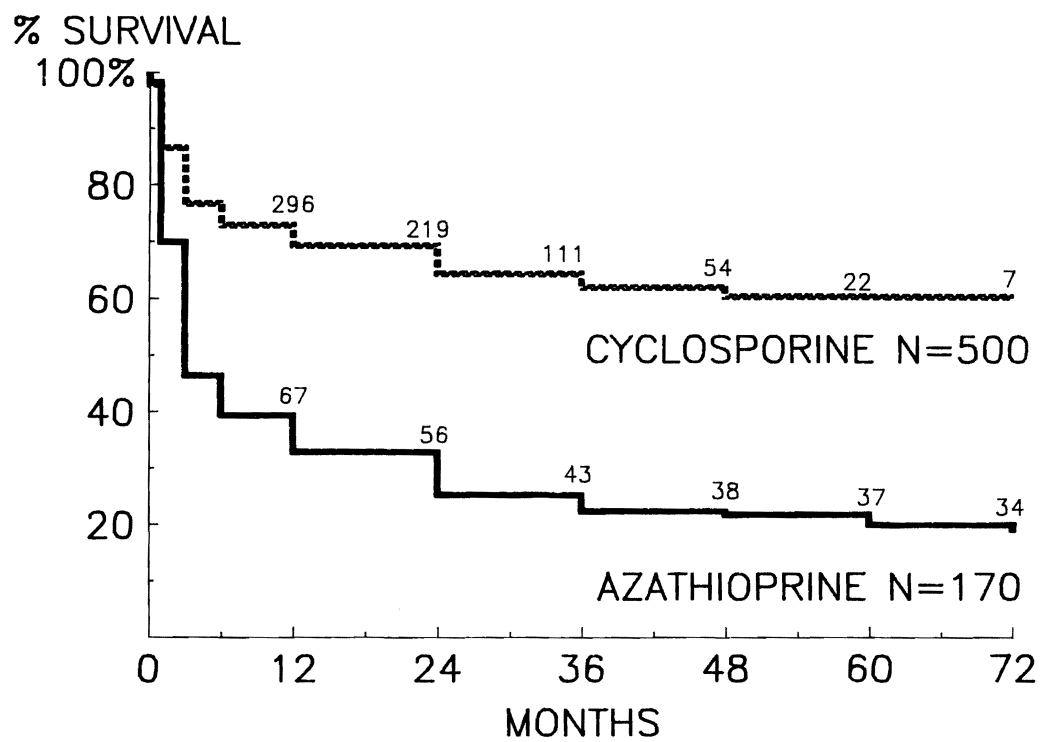


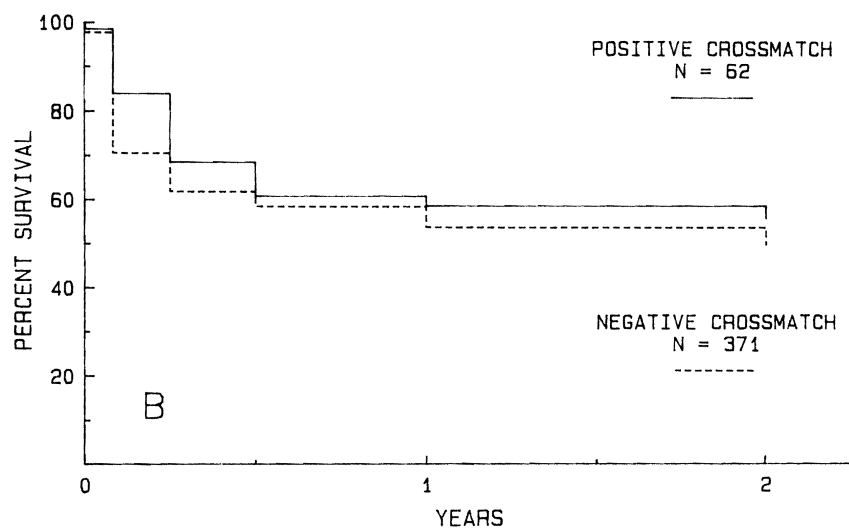
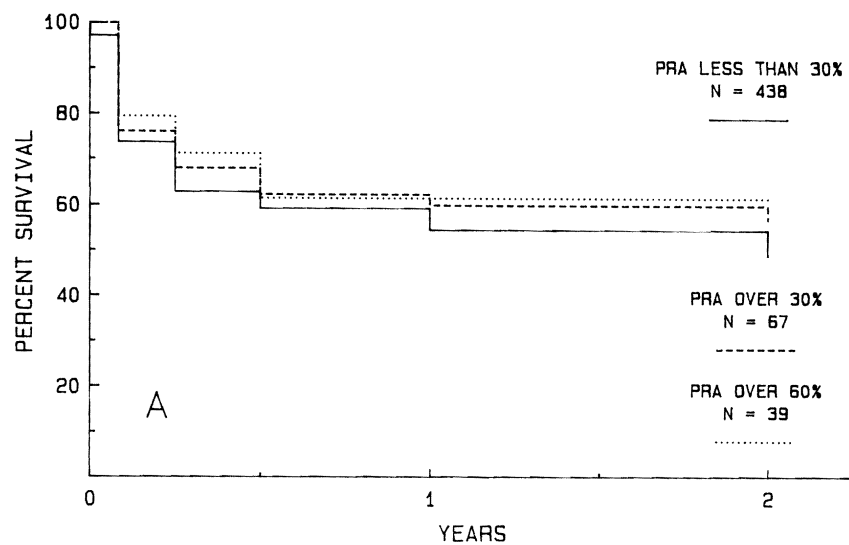




GRAFTS







% SURVIVAL

100%

80

60

40

20

0

12

24

36

48

60

MONTHS

CIRRHOSIS

N = 21

INBORN ERRORS

N = 45

BILIARY ATRESIA

N = 99

14

31

69

8

25

50

3

16

28

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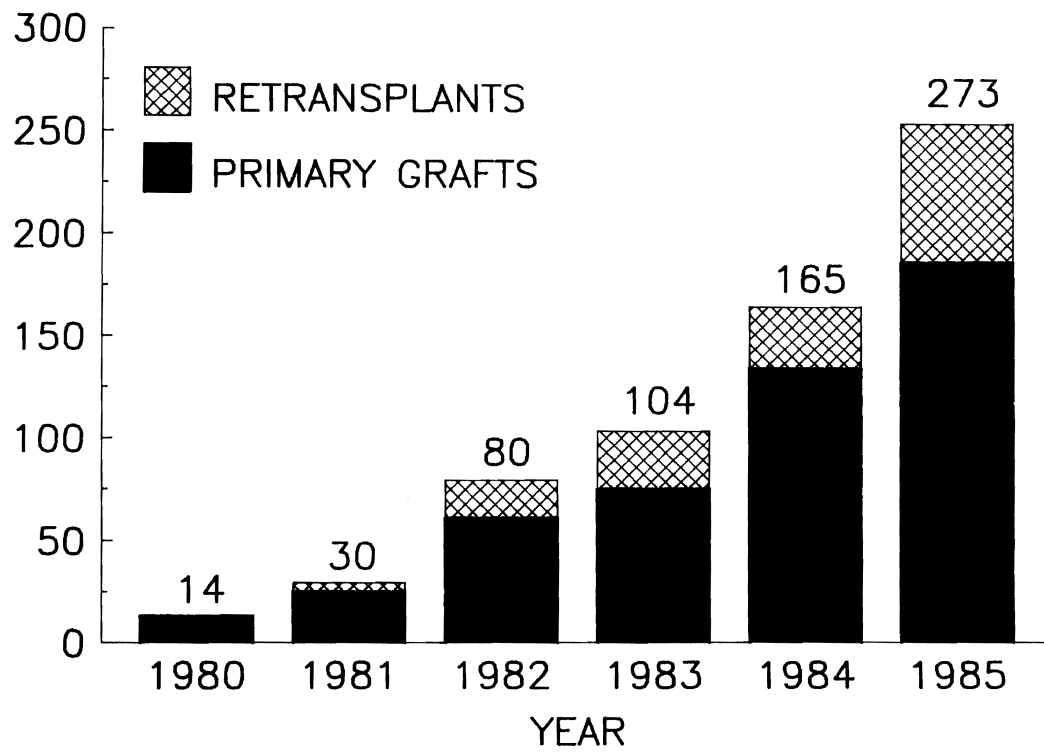
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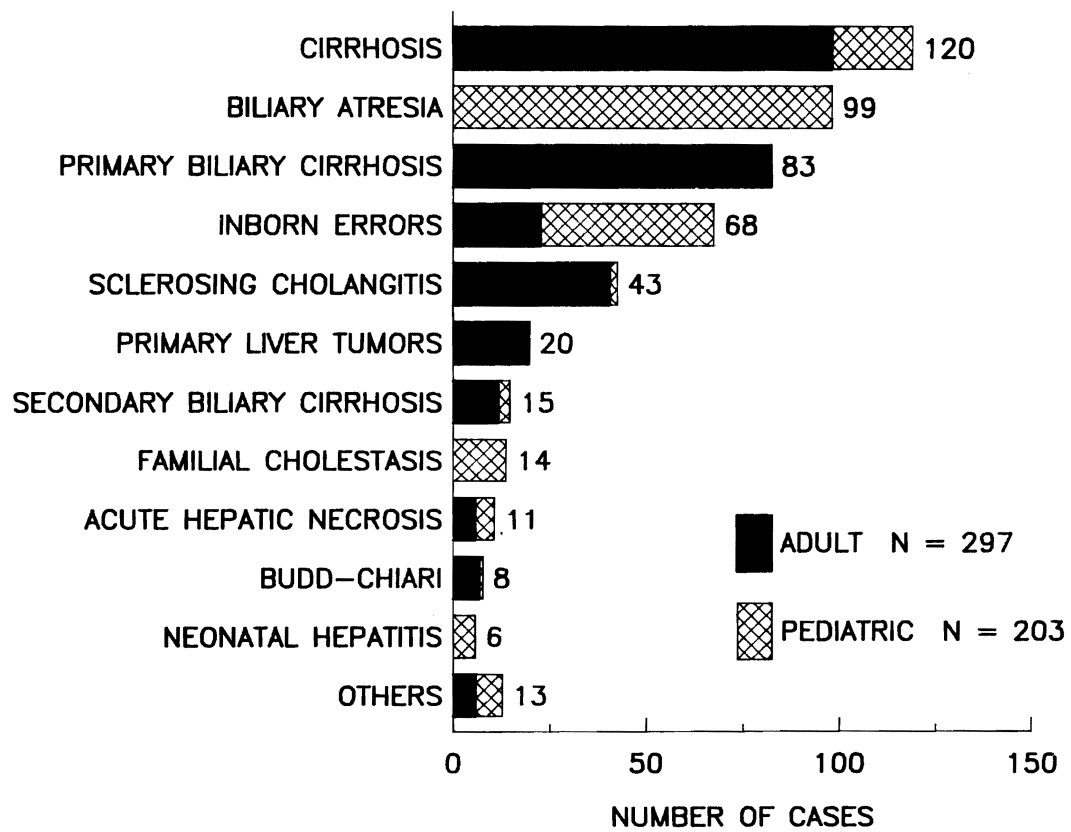
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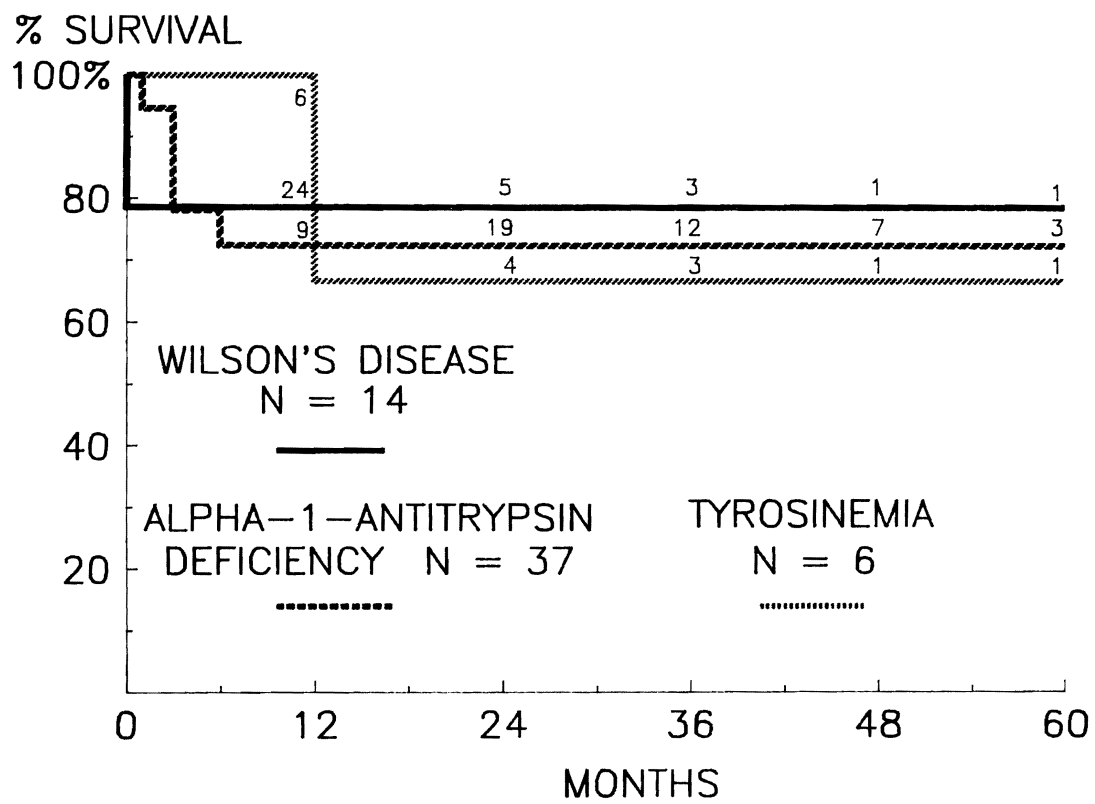
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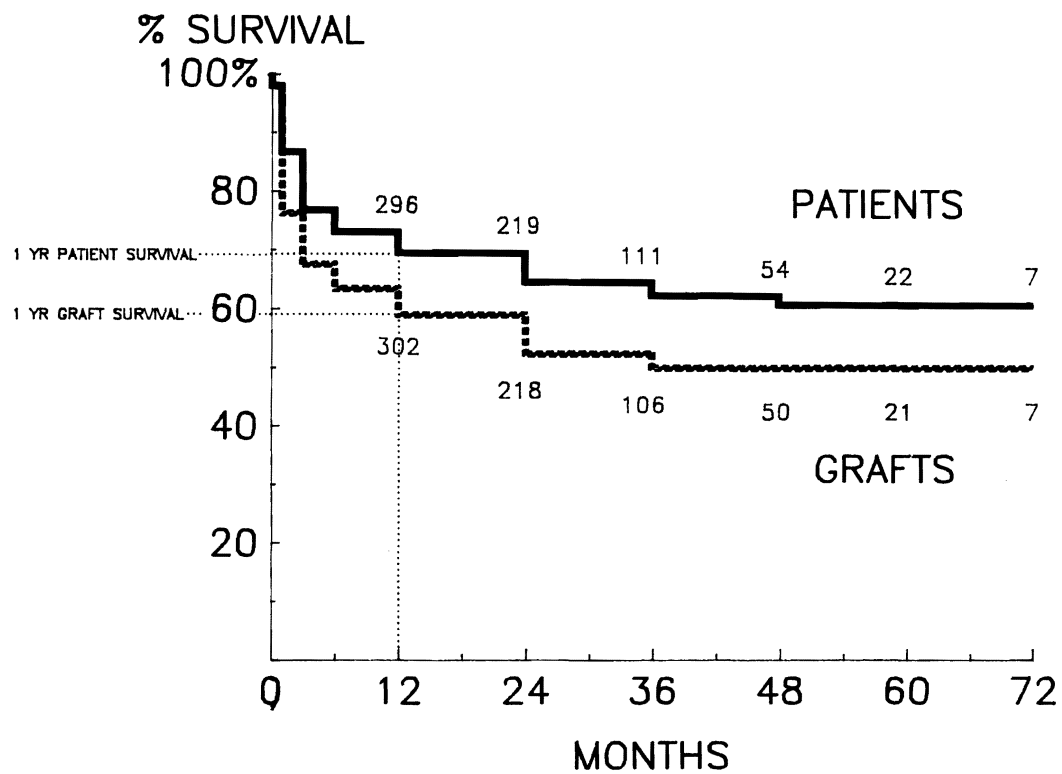
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GRAFTS

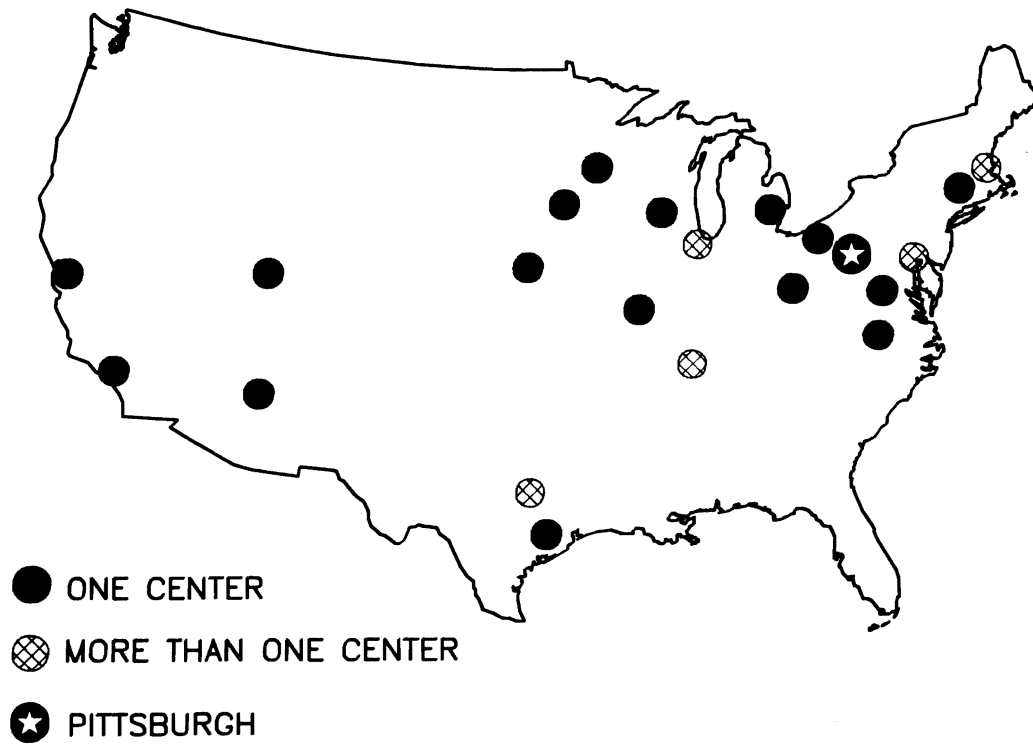


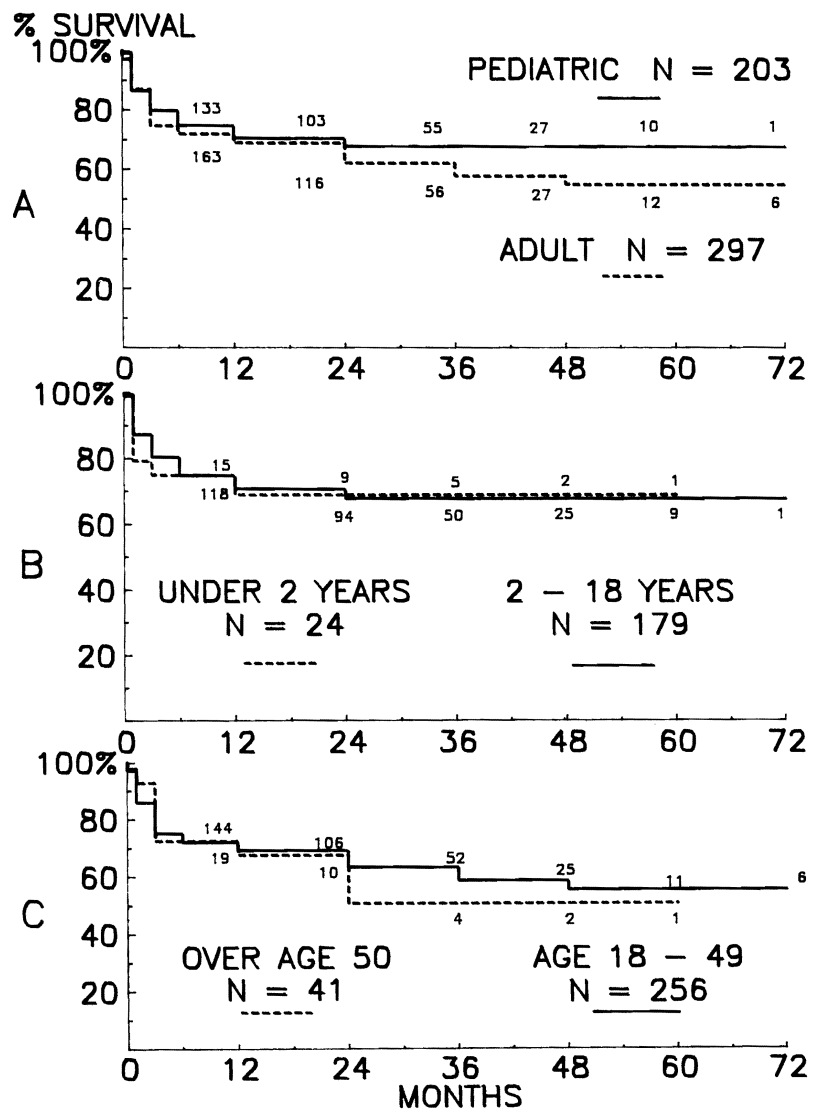






LIVER TRANSPLANT CENTERS IN THE UNITED STATES

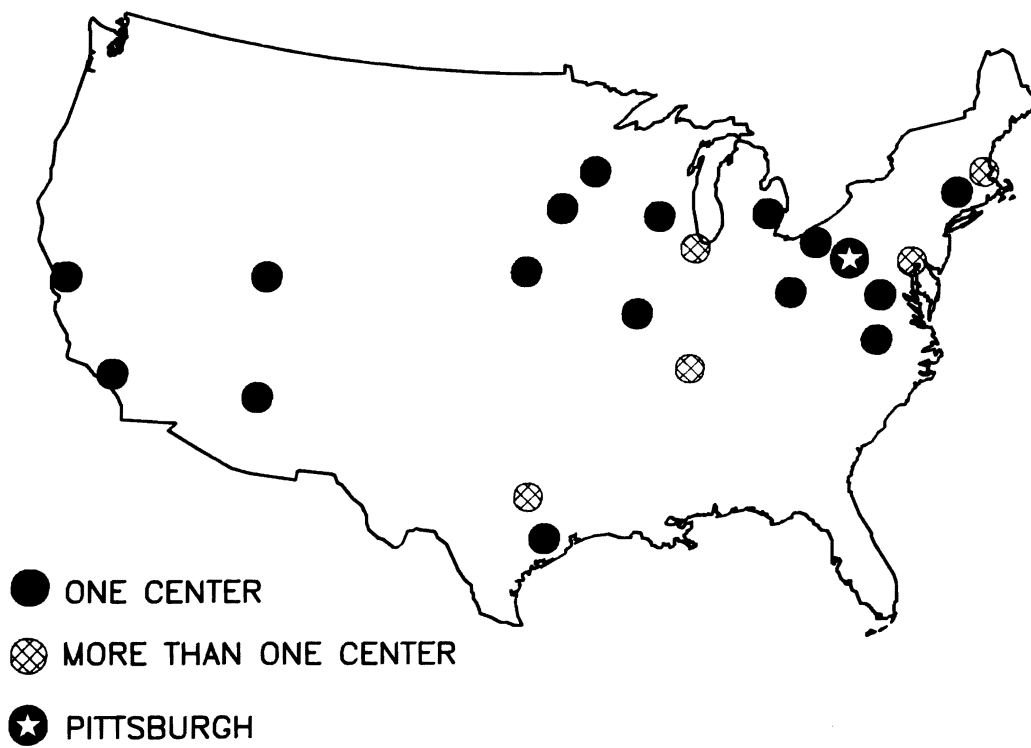


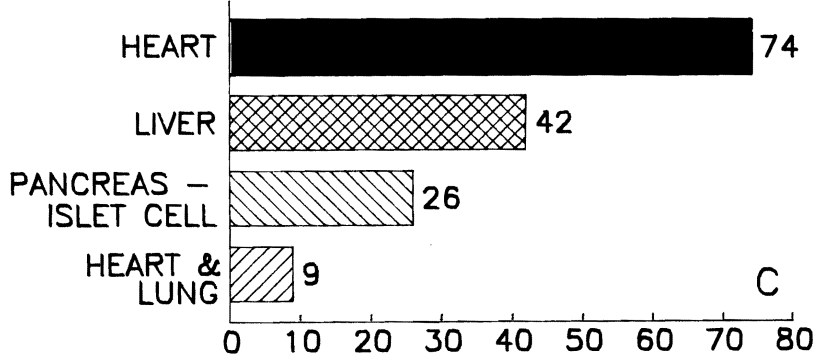
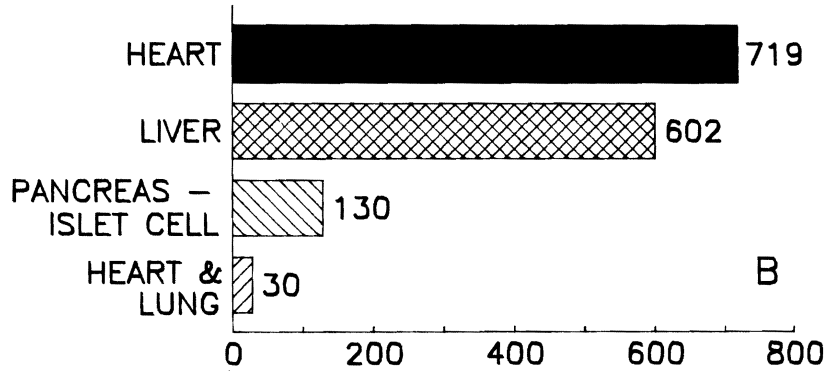
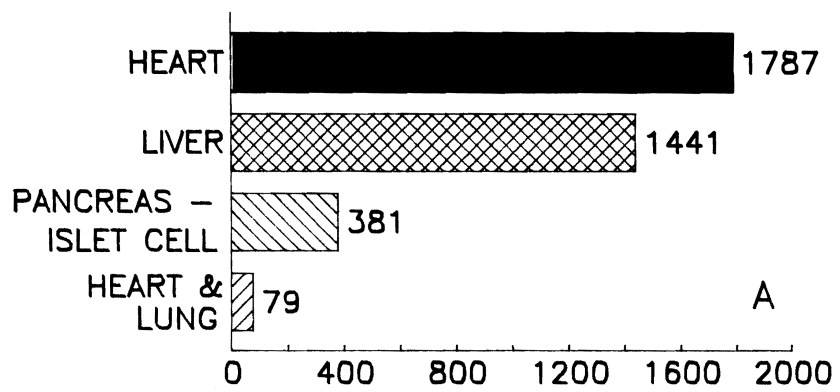


● ONE CENTER

⊗ MORE THAN ONE CENTER

★ PITTSBURGH





FULMINANT FORM

